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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,008	11/17/2003	Masaaki Ikeda	64517.000002	5744

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
07/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/713,008	IKEDA ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-11 and 16-38* is/are pending in the application.

4a) Of the above claim(s) *7-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6 and 16-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

It should be noted that the examiner of record and the art unit of record have changed (see the last page of this office action). The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' response of April 4, 2008, to the non-final action dated October 4, 2007 has been entered. Claims 1, 2 and 20-22 have been amended, and claims 4 and 12-15 cancelled. Claims 32-38 have been newly added. Accordingly, claims 1, 2, 6 and 16-38 are pending in the application. Claims 7-11 stand withdrawn from further consideration, with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Claims 1, 2, 6 and 16-38 are under current examination

New Claim Rejections - 35 USC § 112- New Matter

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 1, 2 and 37 are newly rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art (hereafter the Artisan), that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR §1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The claims encompass methods for proliferating cardiomyocytes and recite introducing proteins or genes to cardiomyocytes using a vector "or other delivery system". The instant specification is devoid of any description for the limitation of "other delivery system", that encompasses the genus of all delivery systems, including those yet to be discovered. Applicants state that support for the amendment appears, at ¶¶ [012], [017], [021], [039], [046] and [048]. While the specification discloses several modes of gene delivery (microinjection, liposome,

calcium phosphate transfection and viral), no support for the genus of other delivery systems is apparent.

Thus, at the time the application was filed, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of "other delivery systems", as claimed.

MPEP 2163.06 notes: "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

This is a new matter rejection.

Response to Claim Rejections - 35 USC § 101

Claims 1, 4, 18, 21, 23, and 24 were rejected under 35 U.S.C. 101, as directed to non-statutory subject matter, in the previous office action dated October 4, 2007. Applicants' cancellation of claim 4 renders its rejection moot. Applicants have amended base claim 1 to recite "recombinant D-type cyclin" and "recombinant cyclin dependent kinase", thus obviating the ground for rejection. Thus, the previous rejection is hereby withdrawn.

Response to Claim Rejections - 35 USC § 102

Claims 1, 4, 18, 21, 23, and 24, were rejected under 35 U.S.C. 102(b) as being anticipated by Soonpaa et al. (Journal of Clinical Investigation, 1997: 99(11):2644-2654), in the previous office action dated October 4, 2007. Applicants' cancellation of claim 4 renders its rejection moot.

Applicants have correctly indicated that Soonpaa et al. fail to teach the active step of introducing a recombinant CD4 or CDK6 cyclin dependent kinase into the nucleus of cardiomyocytes, and thus do not anticipate the instant claims. Accordingly, the rejection is hereby withdrawn.

Response and New Claim Rejections - 35 USC § 112- 1st Paragraph (Scope of Enablement)

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 1, 2, 4, 6 and 16-31 stand rejected under 35 U.S.C. 112, first paragraph, because the specification fails to provide an enablement for the full scope of the claimed invention, in the previous office action dated October 4, 2007. Applicants' cancellation of claims renders its rejection moot. The rejection set forth on pp. 4-10 of the previous office action dated October 4, 2007 is maintained in modified form for claims 1, 2, 6 and 16-31, and further applied to newly added claims 32-38 for reasons of record and the commentary provided below.

The enabled scope (i.e. a method of proliferating cardiomyocytes *in vitro* comprising introducing into the nucleus of cardiomyocytes an adenoviral expression vector encoding cyclin D1, D2 or D3 and cyclin dependent kinase CDK4 or CDK 6, wherein said cyclin is operably linked to a nuclear localization signal), has been expanded to include a method of proliferating cardiomyocytes *in vivo* comprising introducing into the nucleus of cardiomyocytes an adenoviral expression vector encoding cyclin D1, D2 or D3 and cyclin dependent kinase CDK4 or CDK 6, wherein said cyclin is operably linked to a nuclear localization signal, wherein said adenoviral expression vector is introduced by direct injection into the myocardium.

The expanded scope of enablement for the instant invention is consistent with the teachings of the instant specification and the 37 CFR §1.132 Declaration by Dr. Koshimizu. Applicants' arguments are moot in view of the enabled in vivo scope indicated.

However, Applicants have failed to address a number of issues still remaining in the pending claims. The issues include the use of any delivery system for introducing the cyclin and CDK genes, as instantly claimed. Base claims 1 and 2 broadly encompass both *in vitro* and *in vivo* delivery of both genes and proteins. The instant specification, Dr. Koshimizu's Declaration and the prior and post-filing art are silent on the proliferation of cardiomyocytes by delivery of

cyclin and CDK proteins to the nucleus of cardiomyocytes by any delivery system or route of administration, including systemic delivery.

With respect to gene delivery, the instant specification exemplifies the delivery of the cyclin and CDK genes via an adenoviral expression vector, by direct administration of the virus to the apical myocardium. Issues relating to cytotoxicity of adenoviral vector delivered systemically have been previously made of record. Further, is well known in the art that any vector (as instantly claimed), that would include naked plasmid DNA delivered systemically would not result in targeted delivery or impart sufficient gene expression. Further, such expression would be transient. Moreover, terminally differentiated, non-replicating cells, such as cardiomyocytes would be refractive to viral infection by retroviruses, that require actively dividing cells as hosts. Thus, any vector or any viral vector would not predictably provide sufficient directed delivery and expression of the cyclin and CDK genes, absent further undue experimentation.

Additionally, new claims 35 and 36 recite calcium phosphate as the delivery system, that has been demonstrated only for an *in vitro* system, and would be incompatible with viral delivery.

Therefore the previous rejection is maintained in modified form for claims 1, 2, 6 and 16-31, and further applied to newly added claims 32-38, for reasons of record and the preceding discussion.

Conclusion

Claims 1, 2, 6 and 16-38 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fereydoun G. Sajjadi, Ph.D.
Examiner, Art Unit 1633

/Anne Marie S. Wehbe/
Primary Examiner, Art Unit 1633